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ScienceDirect
Life Sciences 81 (2007) 1496–1500
Life Sciences
www.elsevier.com/locate/lifescie

Enhanced mortality of rat pups following inductions of epileptic seizures after perinatal exposures to 5 nT, 7 Hz magnetic fields

L.S. St-Pierre [a], G.H. Parker [a], G.A. Bubenik [b], M.A. Persinger [a,*]

[a] Department of Biology, Behavioral Neuroscience Laboratory, Laurentian University, Canada
[b] Department of Integrative Biology, University of Guelph, Guelph, Ontario, Canada N1G 2W1

Received 2 June 2007; accepted 10 September 2007

Abstract

While investigating the effects of weak complex magnetic fields upon neuroplasticity following induction of early epilepsy, an unprecedented increase in post-seizure mortality (76%) was observed for young rats that had been exposed perinatally to 7 Hz magnetic fields with maximum intensities around 5 nT. Pups exposed to less intense or more intense fields of this frequency did not display this magnitude of significant mortality. Perinatal exposure through the maternal water supply to either a putative nitric oxide donor or inhibitor did not affect this mortality. The non-linear relationship between perinatal 7 Hz magnetic field intensity and post-seizure mortality may be considered analogous to the non-linear relationship between the molarity of ligands and their sequestering to receptor subtypes. These unexpected results suggest that exposure to apparently innocuous stimuli during early development may affect vulnerability to stimuli presented later in ontogeny.
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Keywords: Weak magnetic fields; Sudden death; Seizures; Perinatal exposures; Rat; NanoTesla

Introduction

In the pursuit of understanding the mechanisms of sudden death (Persinger et al., 2005) seizures (Persinger et al., 1988) were induced in rat pups (21–23 days) by a single systemic injection of lithium and the cholinergic (muscarinic) agent pilocarpine just before weaning to produce a transient state of physiological instability. During this period they were exposed to weak (1 microTesla) magnetic fields (McKay et al., 2000) that were patterned to interact with the neuroelectrical progression preceding the overt seizures (Persinger et al., 2002). This ontogenetic period had been selected because it was just prior to the maturation (25–30 days) of the hippocampal-cholinergic inhibitory system in the rat (Douglas, 1975).

We observed a conspicuous mortality that we have not observed in more than 1000 rats we have seized in this age range. Rat pups that developed lithium/pilocarpine-induced seizures after they had been exposed perinatally to 7 Hz, 5 nT magnetic fields displayed an enhanced mortality. It was not observed in rats exposed perinatally to stronger or weaker strengths. We report here the treatments that led to this conspicuous, specific mortality.

Several researchers (Blackman, 2006; Persinger et al., 1974) have suggested that exposure to specific patterns of magnetic fields during development leave an "imprint" which might differentially affect the organism's sensitivity in later life to otherwise ineffective stimuli. The mechanisms are not clear but weak (microTesla to milliTesla) power frequency (50 Hz, 60 Hz) and pulsed magnetic fields have been shown to affect the production of nitric oxide (NO) or to interact with the effects of NO (Jeong et al., 2006). Jelenkovic et al. (2006) reported that exposures to extremely low frequency (ELF) magnetic fields increased the production of NO in the basal forebrain and frontal cortices of rats.

To discern how NO might contribute to later vulnerability to chemicals that evoke epileptic seizures, we investigated the potential interaction by adding compounds that facilitated or inhibited NO production to the mother's water supply. One of the biorelevant pathways involving NO includes $NO+O_2^-$

* Corresponding author. Fax: +1 705 671 3844.
E-mail address: mpersinger@laurentian.ca (M.A. Persinger).

0024-3205/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2007.09.013

resulting in $ONOO^-$ (perioxynitrate) which is modified to ONOOH by the addition of a proton which is followed by the formation of water and OH^-. The involvement of reactive oxygen species (ROS) in mediating the biological effects of weak magnetic fields has been suggested by both empirical (Akdag et al., 2007) and theoretical research (Persinger, 2006). In fact Bawin et al. (1996) showed that extremely low frequency magnetic fields increased NO synthesis in hippocampal tissue slices leading to a disruption of rhythmic slow wave activity.

Materials and methods

Animals

In six separate blocks of experiments over a 2-year period a total of 54 albino Wistar female rats obtained from Charles River Breeders (Quebec) were impregnated. They had been maintained in group housing (3/cage) for at least one month before they were placed with a male rat (2 females/male) for two nights. Pregnancy was inferred by sperm plugs. All females were between four and five months at the time of parturition.

Procedure

About one week before the anticipated delivery the female rats were housed in single plastic cages containing corncob bedding. The cages were placed in two aluminum holding racks that would ultimately generate the magnetic fields. From 2 to 3 days before birth to 14 days after birth the pregnant females were given access to either tap water, 1 g/L of L-arginine (Sigma) in the tap water, or 0.5 g of N-nitro L-arginine methyl ester hydrochloride (Sigma) in tap water. L-arginine is considered a contributor to nitric oxide synthesis while a nitro arginine methyl (NAM) compound inhibits NO synthesis. The fluids were refreshed and measured daily (there were no conspicuous differences between fluid consumption for these three treatments). Food was available *ad libitum*. The room temperature was maintained within 1° of 21 °C; the light:dark cycle was 12:12 with onset at 08:30 LT.

Half of the number of females in each of these conditions were exposed to one of two coils each surrounding an aluminum holding rack whose details have been described previously (Dupont et al., 2005) In summary, the perimeter of each rack were 112 cm × 125 cm and was wrapped with 72 turns of 30 gauge American wire resulting in a width of 13 cm. For each block of experiments one of the coils was activated by a 7 Hz-square wave from a Heath Schlumberger function generator whose output was delivered through an attenuator that could maintain the maximum exposure intensity (peak-to-peak) at either 5 nT, 50 nT or 500 nT. The 7 Hz field was selected because of its predominance in nature (Cherry, 2002), such as the Schumann resonance (Konig et al., 1981) generated between the ionosphere and the earth's surface, and within the brain, such as the dominating theta (4 Hz to 7 Hz) activity within the electroencephalographic activity of the hippocampal formation (Winson, 1975).

Even though the two coils were orthogonal (east–west vs north–south orientation) within the room and were separated by 2 m, an induction occurred within the non-activated coil. According to a MEDA FM 300 Vector magnetometer, the maximum "induced" fields (peak-to-peak) within the non-activated coil from the activated 5, 50, and 500 nT fields were <1 nT, 2 nT, and 10 to 12 nT, respectively. Direct measurement with the magnetometer indicated that the strength of the applied fields within the plastic cages containing the pregnant females was not attenuated.

During all experiments the sensor for the magnetometer was maintained within a plastic cage and wire top, identical to the mothers' exposure cages, while local magnetic field measurements for the *X* (direction of the applied field: 13,800 to 14,200 nT), *Y* (perpendicular to the applied field: 18,850 to 21,000 nT), *Z* (vertical: 39,200 to 41,800 nT) components and the declination and inclination were sampled and stored every 24 s on a laptop computer. The presence of the experimental field was verified by the continuous magnetometric record as well as several times during the day and night by placing a magnetic coil for telephone recording coupled to an acoustic amplifier into the coil containing the cages in order to hear the magnetic signature of the 7 Hz pulse.

Following birth the numbers of pups per litter were monitored daily with minimal disturbance. At 14 days of age the magnetic fields were discontinued and all mothers and litters were given tap water. Between approximately 21 and 23 days of age, before weaning and separation from the littermates and mothers, randomly selected male and female pups from each of the 6 perinatal magnetic field conditions and 3 drug treatments (total $n=108$) were injected sub. cu. with 3 mEq/kg of lithium chloride (3 mEq/cc) before the onset of the scotophase. Four to five hours later between midnight and 01 h and in red light conditions (Michon and Persinger, 1997) each rat was then injected sub. cu. in the opposite hindflank with 30 mg/kg of pilocarpine.

Acute magnetic field exposures and induction of seizures

The rats were then randomly assigned to one of the three "acute" magnetic field conditions within identical plastic cages. These conditions were a sham field, a frequency-modulated magnetic field (Thomas et al., 1998) known to enhance "spontaneous" seizures in adult rats in which epilepsy had been induced months earlier by lithium and pilocarpine (Persinger and Belanger-Chellew, 1999), or to a "LTP" (Long Term Potentiation) field pattern (Stewart and Persinger, 2000) that produced robust long term potentiation in hippocampal slices when applied as electric current (Rose et al., 1988). The two acute-exposure fields were generated between pairs of solenoids in each of the three spatial planes for 0.5 s and then simultaneously in all three planes such that one duty cycle was 2 s or 0.5 Hz (McKay and Persinger, 2003). The fields were generated by a Pentium II level computer by converting a series of numbers between 0 and 255 to voltages between −5 V and +5 V and delivering the current through custom made d.c. to a.c. (DAC) converters (McKay and Persinger, 2003) to the circuits that controlled the generation of the fields. According to a Metex 3800 multimeter and the magnetic sensor probe (Electric Field Measurements, Stockbridge, MA), the

strength of the field within the exposure area ranged between 1 microT and 5 microT.

Following the onset of the overt seizures, defined as rearing and rapid forelimb clonus followed quickly by conspicuous myoclonus (Racine, 1972), the rats were injected sub. cu. with 25 mg/kg of acepromazine (Atravet, Ayerst Laboratories), a treatment that usually facilitates survivability (Fournier and Persinger, 2004). The rats were exposed to only one of these three acute conditions during the subsequent 1.5 h after the injection of the pilocarpine. This interval was selected because it includes the development of the electrical seizures and the multifocal activation, as inferred by ^{14}C-2-deoxyglucose uptake, during the early states of status epilepticus for this mode of seizure induction (Hanforth and Treiman, 1995). For about 1 h of this period the rats were immobile and sedated because of the effects of the acepromazine. After 1.5 h within the observation chambers the rats were returned to their birth room but placed in additional plastic cages with newspaper to absorb excrement. The numbers of rats that were dead from each perinatal treatment were counted during the subsequent 72 h of recovery (no deaths after that time). During this period water and food mush were available *ad libitum*.

The numbers of mortalities were discerned by hierarchical log-linear analysis as a function of the six perinatal 7 Hz magnetic field intensities, the three chemical conditions, the two sexes and the three acute post-seizure magnetic field conditions. Because the effects from the three chemical conditions were not significant statistically as either main effects or as interactions, these variables were collapsed so that the sample sizes within the 7 Hz magnetic field groups, post-seizure field conditions and sex would be sufficient to discern any subtle interactions as discerned by three way analyses of variance. All analyses involved an SPSS software on a VAX 4000 computer.

Results

According to the results of the log-linear analyses, the number of survivors as a function of perinatal chemical treatment (water, L-arginine, N-methyl arginine), perinatal magnetic field condition (<1 nT, 2 nT, 5 nT, 10 nT, 50 nT, 500 nT), post-seizure magnetic field exposure (sham, frequency-modulated magnetic fields or LTP-patterned magnetic fields) and sex the most powerful two-way interaction ("main effect") was between the post-seizure survival and the intensity of the perinatal 7 Hz field (partial chi-squared (5)=51.44, $p<.001$). The proportions of surviving pups for each of the six intensities are shown in Fig. 1.

There was no direct effect from the chemical consumed by their mothers (chi-squared(2)=3.27, $p>.05$) nor an interaction between the chemical consumption and intensity of the field [chi-squared (10)=4.24, $p>.05$]. However there was a statistically significant interaction between the proportion surviving, the intensity of the perinatal magnetic fields and the post-seizure fields [partial chi-squared(10)=19.07, $p<.05$] and the proportion surviving, the intensity of the perinatal field and sex [partial chi-squared (5)=16.56, $p<.01$].

Post hoc partial chi-squared analyses indicated that the first interaction was due to greater mortality if the pups had been exposed to the 5 nT, 7 Hz perinatal field and then LTP-patterned (100%) and frequency-modulated (90%) acute fields immediately after induction of the seizures compared their sham-field controls (50%) and to all other combinations of rats exposed perinatally to less than 5 nT or more than 5 nT (0% to 18%). *Post hoc* chi-square analyses for the second interaction indicated that more females (89%) than males (74%) that had been exposed perinatally to the 5 nT fields died after the seizure compared to males and females in any other of the perinatal intensities for which the male: female ratio was 1.5:1.

Three way analysis of variance for mortality (no, yes) as a function of perinatal magnetic field intensity, post-seizure field treatment and sex was completed to facilitate clarity and comparison. Only the magnetic field effect was statistically significant [$F(5,72)=16.59$, $p<.001$; eta=.67] as a main effect. The *post hoc* analyses even with nominal data showed that the effect was due to the greater mortality in rats that had been

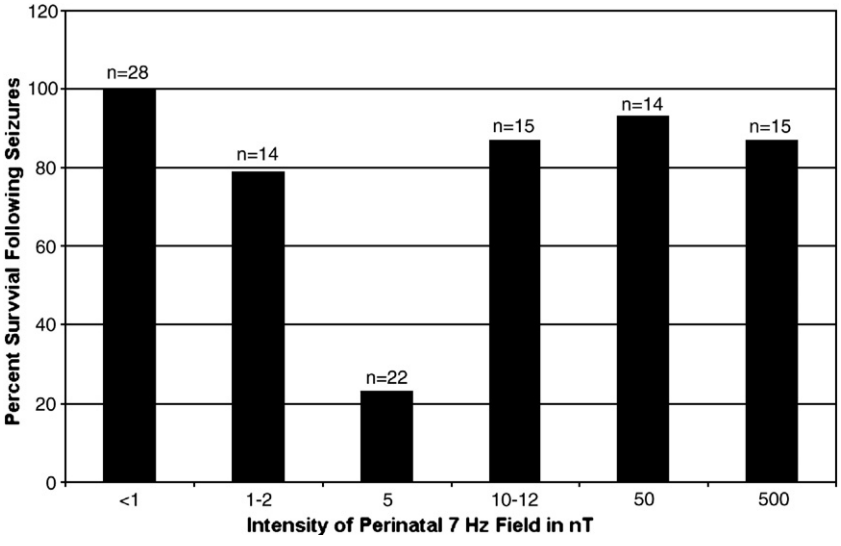

Fig. 1. Percentage of rat pups surviving the induction of epileptic seizures by systemic injection of lithium/pilocarpine and the intensity (in nanoTesla) of the perinatal exposure to 7 Hz-square wave magnetic fields. Numbers in each bar refer to the number of rat pups in that condition.

exposed perinatally to the 5 nT, 7 Hz fields. There was neither a main sex effect [$F(1,72)=.68$, $p>.05$] nor a post-seizure magnetic field effect [$F(2,72)=.37$, $p>.05$]. The only statistically significant interaction [$F(10,72)=2.02$, $p<.05$], which was between the perinatal intensity and the acute, post-seizure magnetic field exposures, was due to the greater *mortality* in rats exposed to the frequency-modulated (89%) or LTP-patterned (100%) field compared to the sham field (50%) for rats that had been exposed to the 5 nT, 7 Hz field whereas these values except for those that had been exposed to the 2 nT, 7 Hz fields and exposed to sham field after seizure (50%) ranged between 0% and 18%.

Discussion

We did not expect that exposure to such weak magnetic fields within such a narrow window of intensity would produce approximately 80% mortality in young rats in which cholinergic seizures were precipitated. Yet, more than a week after the removal of all chemical and magnetic field treatments the weanlings that had been exposed continuously from before birth to about 14 days after birth to 7 Hz magnetic fields with intensities greater than 1 nT and less than 12 nT showed a marked increase in mortality. Rat pups that had been exposed to less intense or more intense magnetic fields did not display this proportion of mortality.

Whereas most adult (>80 days of age) male rats die within 24 h (and certainly within 72 h) without appropriate treatment, usually after periods of cardiac arrythmia (Harrigan et al., 1994) similar to that described by Oppenheimer et al. (1991), preweaned rat pups usually do not. The likelihood that our observations were biased by single litters is unlikely because a total of 11 different litters over three different blocks (74%, 80%, 75% mortality, respectively) were sampled from the 5 nT treatments. In addition, such mortality for this age has not been observed previously in our laboratories.

We had anticipated enhanced mortality of exposure to the acute, physiologically-patterned magnetic fields within the microTesla range following induction of seizures by lithium and pilocarpine (Persinger et al., 2005). We had hypothesized that exposing pups *during* a period of physiological instability (such as the approximately 10 min to 30 min of heterostasis preceding overt stereotyped motor seizures) to the frequency-modulated magnetic fields would have produced greater mortality. Although this (as well as increased mortality for rats exposed to the LTP-patterned field) was observed, the effect was relatively weak compared to the specific mortality for the rats that had been exposed to the 5 nT, 7 Hz magnetic fields perinatally.

It is interesting that the strongest correlation between Sudden Infant Deaths, or SIDs, (Byard and Krous, 2003) in Canada over a 10 year period was associated with the number of days per month that contained global geomagnetic activity within the 1 to 10 nT range (O'Connor and Persinger, 1997). If incidental exposure to this "narrow band" of intensity during the critical postnatal period of 2 months to 8 months is followed by conditions that promote limbic electrical lability, such as fever, then the probability of sudden death might increase. The concept of a predisposing "structural" state that must precede the precipitating stimulus for a SIDs event has been voiced for many years by Eckert (1992).

The mechanisms by which the approximately 5 nT, 7 Hz magnetic field increased the vulnerability to mortality are not clear. They may involve the brain, the heart or any other organ or a combination of organs. Although Durand-Manterola et al. (2001) have shown that micropulsations and geomagnetic phenomena within the nanoTesla range can induce biologically relevant currents within cells, such profound effects from continuous exposure to such weak fields would appear counterintuitive. Yet the efficacy of many receptor subtypes in cellular membranes is also dependent upon extraordinarily minute femtomole to picomole concentrations of ligands that traditionally defied "rational" explanation. The relationship between the magnitude of effect and dosage is clearly non-linear and displays an analogous "window effect". It may be relevant that 28.0 GHz Larmor frequency of an electron (Burke, 1986) at 1 Tesla might be expected to be 28 Hz at 1 nT and approaching 7 Hz around 4 nT, the intensity that produced the maximum mortality in our study.

We suggest that non-classical approaches (Persinger, 2006) should be considered. The seizures were associated with significant utilization of energy. Diminished availability of adenosine triphosphate (ATP) would have interfered with the organs' capacities to recover from the status epilepticus. Inorganic phosphate is derived from phosphoric acid (H_3PO_4) which is ultimately transformed to phosphoanhydrides of -1 or -2 valence that compose the high energy bounds of ATP (Alberts et al., 2002).

If the Liboff–McLeod (Liboff et al., 1987) cyclotron resonance model is applied for static field strengths for a 7 Hz field for PO_4 the solution is about 41,800 nT for -1 valence and 20,900 nT for -2 valence. These values are within the range of the Y and Z components (both perpendicular to the applied field) of the geomagnetic field in the present study. More intense 1 uT or 100 uT, 50 Hz magnetic fields applied through a mu-metal chamber (that would reduce the static field strength substantially and change the resonance solution) can cause uncoupling of inhibitory adenylyl cyclase mediated by melatonin 1a receptors in sensitive cells (Ishido et al., 2001). Hogan and Wieraszko (2004) found that exposure of mouse hippocampal slices to mT range magnetic fields at 0.16 Hz for 30 min not only amplified evoked potentials but produced a four fold increase in cyclic AMP.

Acknowledgements

This research was supported by grants from the Canadian Foundation for the Study of Infant Deaths for the years 2004 and 2000 (Dr. S. Segal Research Grant).

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